# Neuroleptic Malignant Syndrome: Can Be an Unrecognized Chronic Fatal Disease

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ABSTRACT

This case report concentrates on the fatal consequences of the chronic aspects of neuroleptic malignant syndrome (NMS). It is a life-threatening side effect and has been identified since antipsychotics were developed. Efforts to highlight the propensity to develop NMS for those more sensitive to psychotropic medications have been infrequent. Ethnic groups, such as Asians and African Americans, seem to be at higher risk, and therefore clinicians must be hypervigilant of NMS with these groups. Strategies on how to keep a heightened level of awareness about the use of traditional antipsychotic medications with those at risk for NMS are discussed.

**KEYWORDS**: Neuroleptic malignant syndrome, antipsychotic medications, psychiatric inpatients, chronic illness, risk, creatine phosphokinase (CPK)

Neuroleptic malignant syndrome (NMS) is a rare and potentially fatal adverse drug reaction.[1] This case report describes the challenges of treating psychiatric patients with the possibility of NMS. Clinicians need information about NMS, including discussions about the fragility of patients with serious and persistent mental health issues. Additional aspects to be taken into account are the cultural and racial features within unique populations, such as Asians and African Americans. This case helps to clarify the criteria and promote early identification of the presence of NMS.

## CASE REPORT

Mr. R. was a 45-year-old African American male with a history of psychosis and behavioral problems who was diagnosed with schizophrenia. Upon admission to a state psychiatric inpatient facility in 2017, he demonstrated paranoid psychotic symptoms, such as being convinced clinicians were plotting to kill him, bizarre posturing, and selective mutism. Other symptoms included tactile and auditory hallucinations, delusions about being poisoned, as well as being religiously preoccupied. Upon admission, Mr. R. was administered oral, and subsequently added decanoate, haloperidol. He was also treated with different first- and second-generation antipsychotics with only minimal improvement. He experienced significant extrapyramidal side effects (EPSE) in response to all antipsychotics. Mr. R. also had numerous medical conditions, including hypothyroidism.

This patient was on antipsychotic medication for at least six months and was still psychotically symptomatic when he became incontinent of urine and stool, as well as lethargic, with a low-grade fever and rapid heart rate. He was hospitalized in a general hospital to rule out sepsis, hypoglycemia, and hypotension. His creatine phosphokinase (CPK) was 1,281, and his diagnosis at the time was gastroenteritis with a hypoglycemic and hypotensive episode; however, with subsequent information and episodes, this might have been a missed episode of NMS.

Upon Mr. R.'s return to the inpatient psychiatric center, he remained symptomatic and was again treated with haloperidol 5mg. His EPSE were treated as well. Rigorous medical testing returned no acute findings. There was a notable abatement of his psychotic symptoms for a period of two months until he became more delusional and paranoid. He was found cowering on the floor, cringing and covering his head, actively reacting to psychotic symptoms. Oral haloperidol was increased from 5mg bid to 10mg bid. Despite the increased dosage, he continued to be psychotic with fixed delusions and angry behavior. Other options were being considered to treat Mr. R., including electroconvulsive therapy (ECT) and treatment with clozapine (due to its lowest incidence of NMS). Mr. R. had a naturally low ANC; however,

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his bone marrow could have been supported medically. Therefore, clozapine remained under consideration.

Within one week of the oral haloperidol dosage increase, Mr. R. was moving slowly, incontinent of urine and stool, nauseous, and refusing to answer staff questions. His blood pressure was low normal, temperature was 101.6°F, and he had significant muscle rigidity. He was hospitalized again at a general hospital. Laboratory results at the time included a CPK of 900, and a diagnosis of NMS was made. Mr. R. was removed from psychotropic medications and given intravenous (IV) fluids.

Following his treatment at a general hospital for this second episode, Mr. R. returned to the inpatient psychiatric center. The usual after care for NMS was instituted, including withdrawal of all antipsychotic medication and adequate nutrition and hydration. Metabolic challenges are considered to be contributory to the risk of developing NMS. Anecdotal publications in the literature described how effective these interventions are under the circumstances.[2]

Even though all antipsychotic medication had been discontinued following this latest episode of NMS, Mr. R. did show some psychiatric improvement. When Mr. R. was considered to be medically cleared to resume antipsychotic medication, he refused all oral and injectable antipsychotic medication. He denied mood or psychotic symptoms and observations of his behavior and interactions indicated significant resolution of his psychosis as well. His unusual presentation of not being psychotic, even though he was not being recently medicated with antipsychotic medication, continued for weeks. It was supposed that there was a continued impact of previous antipsychotic treatment.

Then, abruptly after weeks without antipsychotic medication, Mr. R. started exhibiting significant psychosis. He stopped eating and drinking, believing he was being poisoned, regularly responded to internal stimuli, isolated himself, and was agitated and threatening. Psychosis now included tactile hallucinations of snake bites and head staples. Treatment with an antipsychotic for his refusal to eat and potential violence was required and administered for three months with little effect. During this time, Mr. R. appeared medically stable. Despite his medical status, he was found unresponsive in his room. After emergency response interventions proved unable to resuscitate him, Mr. R.'s death was pronounced in 2018.

On autopsy, there was evidence of rhabdomyolysis, acute renal tubular epithelial injury due to myoglobinuria, and severe acute fibrinous pericarditis. It is notable that Mr. R.'s electrocardiogram (ECG) prior to his death was normal and did not show evidence of cardiac dysfunction. There was no complaint of chest pain or shortness of breath, and on examination there was no lung congestion or fluid on auscultation. The autopsy determination was that Mr. R. died from NMS.

## CONCLUSION AND RECOMMENDATIONS

We recommend high awareness about the use of antipsychotic medications with those at risk for NMS. Acute NMS is commonly known; however, whether the chronic effect of NMS also can be fatal is less known and was the outcome of this case. Antipsychotic medications can be problematic with those who have medical comorbidities. The dilemma is to determine the best possible option for patients who are at-risk among the choices available using clinical judgment and case reports such as this.

Mr. R., an African American, was extremely sensitive to a variety of neuroleptics. Ananth et al[3] explicitly states certain minority groups, one of which Mr. R. belonged to, are more prone to metabolic difficulties, including cardiac, renal, and neurological abnormalities. Furthermore, clinicians need to be attuned to the differential receptor-mediated responses in these groups to prevent toxicity of those drugs whose metabolism is catalyzed by polymorphic isoenzymes.[4] NMS might be increasingly relevant beyond psychiatric settings, specifically for intensive care unit (ICU) practitioners, given the frequent administration of antipsychotics to patients who are critically ill for agitated delirium.[5]

Masi et al[6] notes the massive asymptomatic creatinine kinase elevation (MACKE) present in adult psychiatric patients without signs of NMS. Since this is what occurred with Mr. R., it supports the importance of routine checking CPK levels. Timing for this testing could be at initiation, dosage increases, and on augmentation with a second or further antipsychotic. Hermesh et al[7] examined CPK levels and found statistical significance in patients with psychotic symptoms and NMS with only CPK in the upper limit of normal range. Although it might be counterintuitive, there is literature discussing normal CPK levels in those with NMS.[8]

Patients sensitive to antipsychotics while floridly psychotic might need rechallenging with an antipsychotic coupled with careful and close monitoring. A patient who has experienced NMS would warrant regular monitoring of CPK levels. One recommendation is to monitor CPK levels as is done for metabolic syndrome with which to regularly assess the patient's status. The laboratory values might not have the remarkable elevations typically propelling a diagnosis of NMS yet have clinical value in this population. Assure the CPK levels do not approach the levels obtained when the patient had an acute episode of NMS as any elevation of CPK has a deleterious effect on the heart and kidneys and can precipitate a fatal outcome. ECG and cardiac isoenzyme monitoring on an individual basis could avoid an unrecognized untoward effect of an antipsychotic medication.

Employing alternative treatments, such as ECT, psychological interventions, behavioral interventions, supportive environment, and hospitalization, could prolong life.[9] The risk-benefit of continuing any pharmacological intervention given any metabolic threat determined from laboratory results can provide guidance in determining clinical approaches. Genetic testing to ascertain responsivity to a particular agent could be most helpful. If patients are willing to participate in genetic testing, this could indicate whether a particular medication demonstrated sensitivity and responsiveness. Would the medication be a problem or be effective, especially around first episode and initial medication trials? Additionally, this action might contribute to a more sophisticated aspect of conducting a clinical history.

Common tests for detecting NMS include complete blood count (CBC), serum CPK, a basic metabolic panel, brain computed tomography (CT) scan, brain magnetic resonance imaging (MRI), myoglobin levels, urinalysis, urine culture, blood culture, lumbar puncture, toxicology screen, and chest x-ray. Biomarkers, such as creatinine levels and heart evaluation via ECG, could be critical aspects of tracking functioning. While all of these tests might

not be easily accessible or agreed to, valuable information can be gleaned from obtaining baseline and follow-up tests to whatever degree possible. With this population, this regular infusion of data can be most useful in tracking response, metabolic impacts, and threats.

Prescribers need to be diligent about the acute and chronic effects of NMS. If a patient manifests minimal signs of neuromuscular side effects and is in the category of high-risk (African American, Asian-American, and geriatric), use of first-generation antipsychotics is recommended sparingly, if at all, and healthcare profressionals should consider alternative treatments. Vulnerable groups are best treated with slower movement on antipsychotic medication changes. How NMS is expressed in minorities is information not readily available in the professional literature and provides an investigative trajectory for clinicians. The outcome of this case provides guidance for psychiatrists that high recognition and surveillance of the enumerated high-risk categories might mitigate negative clinical events.

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